JP 60-004189

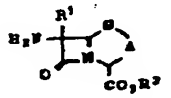
SPECIFICATION

1. TITLE OF INVENTION

PROCESS FOR PREPARING β-LACTAM COMPOUNDS

2. CLAIM

A process for preparing β-lactam compounds, which comprises reacting a compound of the formula:

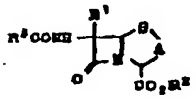


(I)

[wherein A is $-C(CH_3)_2-$ or $-CH_2-CB=$ (in which B is a hydrogen atom, a halogen atom, an alkoxy group, a vinyl group or $-CH_2D$ (in which D is a hydrogen atom, a halogen atom, an alkoxy group, an acetoxy group, a carbamoyloxy group, an alkylthio group, an aromatic heterocycle-thio group or a pyridinio group)), R^1 is a hydrogen atom or an alkoxy group and R^2 is a hydrogen atom, a metal atom or an ester residue] with a carboxylic acid or its salt of the formula:

R^3COOR^4

[wherein R^3 is an acyl group and R^4 is a hydrogen atom, a metal atom or an ammonium ion] in the presence of phosphorus oxychloride to give a compound of the formula:



(II)

[wherein A, R^1, R^2 and R^3 are each as defined above].

3. DETAILED EXPLANATION OF INVNETION

The present invention relates to a process for preparing a β-lactam antibiotic derivative by acylation of an amino group in a β-lactam antibiotic substance.

A variety of β-lactam antibiotic substances obtainable by acylation of an amino group in β-aminopenicillanic acid or γ-aminocephalosporanic acid derivatives exhibit excellent anti-microbial activity and are used widely as anti-microbial agents. For acylation of an amino group in β-aminopenicillanic acid or γ-aminocephalosporanic acid derivatives, there are known many methods, which include acid chloride method using phosphorus pentoxide or thionyl chloride, Vilsmeyer method using DMF-$POCl_3$, mixed acid anhydride method with isobutyloxycarbonyl chloride, activated esterification method with N-hydroxybenzotriazole-DCC or triphenylphosphine-diethylazodicarboxylate, etc.

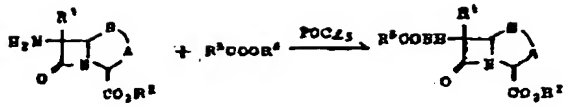
Said acylation methods are defective in having strict limitation on the reaction temperature and the solvent to be used and being apt to cause side reactions. For instance, the double bond at the 3-position of cephalosporins is rearranged to the 2-position; an oxime group in an acylating agent is isomerized from the syn form to the anti form; a tert-butoxycarbonyl group as an acyl-protective group is so weak to an acid that elimination of the protective group takes place, etc. Due to such side reactions, conventional acylation methods make frequently the isolation of the objective product troublesome. Also, the activated esterification method using, for instance, N-hydroxybenzotriazole-DCC or triphenylphosphine-diethylazodicarboxylate produces the by-products originated from the reagents in addition to said side reactions, whereby separation of the objective product becomes difficult.

In order to overcome the above defectiveness, the present inventors have investigated extensively on various methods for acylation of the amino group in β-lactam antibiotic substances and found that the acylation with phosphorus oxychloride facilitates the reaction operation and does neither cause said side reactions nor produce any hardly separable by-products from the reagent. Thus, it provides a very excellent acylation method. This invention is based on the above finding.

In the formula (I), R^1 is a hydrogen atom or an alkoxy group such as methoxy or ethoxy, and R^2 is a hydrogen atom, a metal atom (e.g. lithium, sodium, potassium) or an ester residue. Examples of the ester residue are a carboxyl-protecting group which is not limitative and includes any group usually employed for protection of a carboxyl group in β-lactam antibiotic substances (e.g. tert-butyl, benzhydryl, 2,2,2-trichloroethyl, aryl, p-methoxybenzyl, p-nitrobenzyl, trimethylsilyl, methoxy-methyl, benzyloxymethyl, phenacyl), a group of the formula: $-CHR^5CO_2R^6$ wherein R^5 is a hydrogen atom or a lower alkyl group (e.g. methyl, ethyl) and R^6 is a C_{1-6} straight or branced alkyl group (e.g. methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, pentyl, 3-pentyl, tert-pentyl, hexyl, 3-hexyl) or a C_{1-6} cycloalkyl group (e.g. cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl) and a group of the formula: $-CH_2COOR^7$ wherein R^7 is a lower alkyl group (e.g. methyl, ethyl, propyl, isopropyl, isobutyl, sec-butyl, isobutyl, tert-butyl) or a cycloalkyl group substituted with lower alkyl (e.g. 1-methyl-1-cyclopentyl, 1-methyl-1-cyclohexyl, 1-ethyl-1-cyclopenxyl).

A is $-C(CH_3)_2-$ or $-CH_2-CB=$ in which B is a hydrogen atom, a halogen atom(e.g. fluorine, chlorine, bromine), an alkoxy group (e.g. methoxy, ethoxy, propoxy), a vinyl group or $-CH_2D$ in which D is a hydrogen atom, a halogen atom (e.g. fluorine, chlorine, bromine), an alkoxy group (e.g. methoxy, ethoxy), an acetoxy group, a carbamoyloxy group, an alkylthio group (e.g. methylthio, ethylthio), an aromatic heterocycle-thio group (e.g. 1-methyl-1H-tetrazol-5-ylthio, 1-carboxymethyl-1H-tetrazol-5-ylthio, 1-(2-dimethylaminoethan-1-yl)-1H-tetrazol-5-ylthio, 1,3,4-thiadiazol-2-ylthio, 5-methyl-1,3,4-thiadiazol-2-ylthio, 2,5-dihydro-6-hydroxy-2-methyl-5-oxo-as-triazin-3-ylthio) or a pyridinio group (e.g. 1-pyridinio, 4-carbamoyl-1-pyridinio), etc.

The present invention is concerned with a process for preparing the compound of the formula (III) which comprises reacting the compound of the formula (I) and the compound of the formula (II) using phosphorus oxychloride in the presence of a base.



(I) (II) (III)

In the formula (II), R^3 is

a chloromethyl group;

a dichloromethyl group;

an optionally substituted phenoxymethyl group, the substituent being halogen (e.g. chlorine, bromine), methoxy, nitro or acetoxy present at the o-, m- or p-position);

an aromatic heterocycle-substituted methyl group (e.g. 2-thenyl, furfuryl, 2-protected aminothiazol-4-ylmethyl, the protective group being not limitative and including such conventional ones as trityl, formyl, chloroacetyl, trifluoroacetyl, tert-butoxycarbonyl, 2,2,2-trichloroethoxycarbonyl, benzyloxycarbonyl, p-nitrobenzyloxycarbonyl or allyloxycarbonyl);

a 2-aminothiazol-4-ylmethyl group;

a group of the formula: $R^8CH(NHR^9)$- wherein

R^8 is phenyl;

o-, m- or p-hydroxyphenyl in which the hydroxyl group is optionaly protected with any conventional group such as trimethylsilyl, tert-butyldimethylsilyl, benzyloxycarbonyl, p-nitrobenzyloxycarbonyl, allyloxycarbonyl or 2,2,2-trichloroethoxycarbonyl);

an aromatic heterocyclic group (e.g. 2-furyl, 2-thienyl); or

a group of the formula: $-CHR^{11}-OR^{10}$ wherein R^{10} is hydrogen or a protective group for hydroxyl, the protective group being not limitative and including trimethylsilyl, tert-butyldimethylsilyl, benzyloxycarbonyl, p-nitrobenzyloxycarbonyl, allyloxycarbonyl, methoxymethyl and tetrahydropyranyl and R^{11} is lower alkyl (e.g. methyl, ethyl, propyl, isopropyl), and

R^9 is hydrogen;

a protective group for amino (the protective group being not

limitative and including formyl, acetyl, chloroacetyl, trifluoroacetyl, trityl, tert-butoxycarbonyl, 2,2,2-trichloroethoxycarbonyl, benzyloxycarbonyl, p-nitrobenzyloxycarbonyl and allyloxycarbonyl); or

an acyl group of the formula: $R^{12}CO$- wherein R^{12} is 4-ethyl-2,3-dioxopiperazin-1-yl, 6,7-dihydroxychromon-3-yl, 4-hydroxy-6-methylpyridin-3-yl, 4-hydroxy-1,5-naphthyridin-3-yl or N-3,4-dihydroxybenzoyl)-N-methylamino, the hydroxyl group in these groups being protected with any conventional protective group for hydroxyl such as acetyl, trifluoroacetyl, chloroacetyl, benzoyl, p-nitrobenzoyl, tetrahydropyranyl, methoxymethyl, benzyloxymethyl, trimethylsilyl, tert-butyldimethylsilyl, trityl, tert-butyl, 2,2,2-trichloroethoxycarbonyl, benzyloxycarbonyl, p-nitrobenzyloxycarbonyl or allyloxycarbonyl;

a group of the formula: $R^8R^{15}CH$- wherein

R^8 is as defined above; and

R^{15} is carboxy, protected carboxy (the protective group being not limitative and including tert-butyl, trityl, benzhydryl, trimethylsilyl, tert-butyldimethylsilyl, 2,2,2-trichloroethyl, p-nitrobenzyl, p-methoxybenzyl or allyl) or sulfonyloxy;

a group of the formula: $R^{14}NH$ X

wherein

N -C(=NOR15)-

R^{14} is hydrogen or a protective group for amino, the protective group being not limitative and including trityl, formyl, acetyl, chloroacetyl, trifluoroacetyl, tert-butoxycarbonyl, 2,2,2-trichloroethoxycarbonyl, benzyloxycarbonyl, p-nitrobenzyloxycarbonyl and allyloxycarbonyl; R^{15} is a straight or branched alkyl group (e.g. as methyl, propyl isopropyl) optionally bearing a substituent of 1 to 3 carbon atoms such as methyl, ethyl, fluorine, chlorine, bromine, hydroxyl, acetoxy, dimethylamino or carboxy, which may be specifically $-CH_2CH_2R^{16}$ (wherein R^{16} is fluorine, chlorine, bromine, hydroxyl, acetoxy, dimethylamino or carboxy) or $-CR^{17}R^{18}-CO_2R^{19}$ (wherein R^{17} is hydrogen, methyl or ethyl, R^{18}

is hydrogen, methyl or ethyl and R^{19} is hydrogen or a protective group for carboxy (the protective group being not limitative and including tert-butyl, trityl, benzhydryl, trimethylsilyl, tert-butyldimethylsilyl, 2,2,2-trichloroethyl, p-nitrobenzyl, p-methoxybenzyl or allyl)); and

X is NH, oxygen or sulfur;

the oxime in the formula taking a syn-form; or

a group of the formula: $Z\text{-}CH_2\text{-}CO\text{-}C(=NOR^{15})$- wherein

Z is hydrogen, halogen (e.g. chlorine, bromine, iodine), mesyloxy, tosyloxy or benzenesulfonyloxy; and

R^{16} is as defined above;

the oxime in the formula taking a syn form.

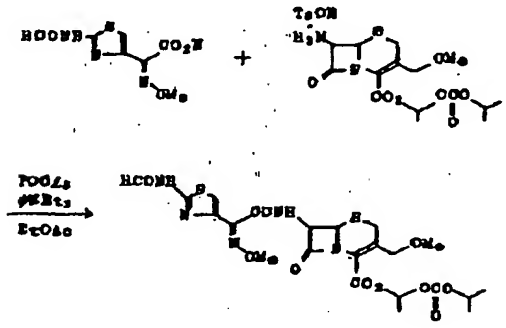
R^4 is a hydrogen atom, a metal atom (e.g. sodium, lithium, potassium) or an ammonium ion such as the one formed from an amine (e.g. dimethylamine, diethylamine, diisopropylamine, dioctylamine, dicyclohexylamine, dicyclohexylisopropylamine, triethylamine, tributylamine, DABCO, N,N-dimethylaniline, N,N-diethylaniline, pyridine, lutidine, collidine, 4-dimethylaminopyridine, quinoline, isoquinoline) with R^3COOH wherein R^3 is as defined for R^3 in the formula (II).

The compound of the formula (I) and the compound of the formula (II) are dissolved or suspended in an organic solvent (which is not limitative and includes aromatic hydrocarbons (e.g. benzene, toluene, xylene), ethers (e.g. diethyl ether, tetrahydrofuran, dioxane), halogenated hydrocarbons (e.g. dichloromethane, chloroform, carbon tetrachloride), acetonitrile, ethyl acetate, acetone, water and their mixtures), phosphorus oxychlordie is added thereto in the presence of 1 to 3 equivalents of a secondary or tertiary amine (which is not limitative insofar as the progress of the reaction is not prevented and includes secondary amines (e.g. dimethylamine, diethylamine, diisopropylamine, dioctylamine, dicyclohexylamine, cyclohexylisopropylamine) and tertinary amines (e.g. triethylamine, tributylamine, DABCO, N,N-dimethylaniline, N,N-diethylaniline, pyridine, lutidine, collidine, 4-dimethylaminopyridine, quinoline, isoquinoline) at a temperature of -30℃ to room temperature, and the reaction is effected for a period of 10 minutes to several hours. Treatment of the reaction mixture by

an ordinary procedure affords the compound of the formula (III) wherein R1, R2, R3 and A are each as defined above, which may be further purified by chromatography, recrystallization or reprecipitation to give the objective product.

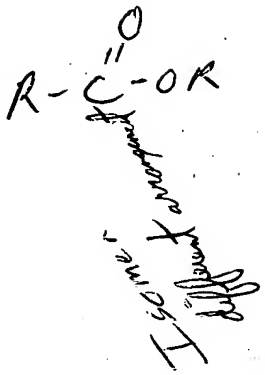
The present invention will be hereinafter explained by way of Examples.

[Example 1]



N-formyl CP

Formula I

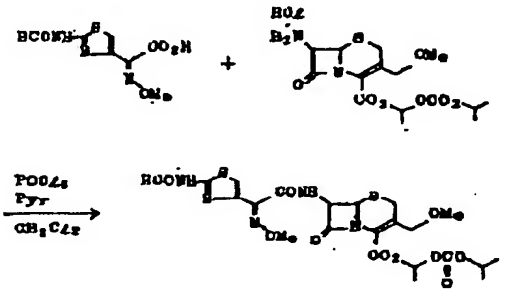


1-(Isopropyloxycarbonyloxy)ethyl 7-[2-(2-formylaminothiazol-4-yl)-(Z)-2-methoxyimino-acetamido]-3-methoxymethyl-3-cephem-4-carboxylate (Isomer A based on the ester portion)

2-(2-Formylaminothiazol-4-yl)-(Z)-2-methoxyiminoacetic acid (252 mg) and 1-(isopropyloxycarbonyloxy)ethyl 7-amino-3-methoxymethyl-3-cephem-4-carboxylate p-toluenesulfonate (Isomer A) (547 mg) are suspended in ethyl acetate (6 ml), N,N-diethylaniline (478 mg) is added thereto, and the resultant mixture is cooled to -10℃. A solution of phosphorus oxychloride (169 mg) in ethyl acetate (1 ml) is dropwise added thereto, followed by stirring at the same temperature as above for 20 minutes. The reaction mixture is washed with dilute hydrochloric acid, 5 % aqueous sodium hydrogen carbonate solution and an aqueous sodium chloride solution in order, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue is washed with diisoproopyl ether and collected by filtration to give said objective compound (537 mg).
NMR (δ ppm, deuteroacetone):

1.28 (6 H , d , J = 6 Hz) , 1.54 (3H , d , J = 5.5 Hz) , 3.28 (2 H , s) , 3.58 (2 H , s) , 3.98 (3 H , s) , 4.23 (2 H , s) , 4.62 (1 H , Hep , J = 6 Hz) , 5.15 (1 H , d , J = 5 Hz) , 5.91 (1 H , dd , J = 9 Hz , J = 8 Hz) , 6.78 (1 H , q , J = 5.5 Hz) , 7.32 (1 H , s) , 8.38 (1 H , d , J = 9 Hz) , 8.58 (1 H , s)

[Example 2]



1-(Isopropyloxycarbonyloxy)ethyl 7-[2-(2-formylaminothiazol-4-yl)-(Z)-2-methoxyimino-acetamido]-3-methoxymethyl-3-cephem-4-carboxylate (Isomer B based on the ester portion)

[2a]

2-(2-Formylaminothiazol-4-yl)-(Z)-2-methoxyiminoacetic acid (252 mg) and 1-(isopropyloxycarbonyloxy)ethyl 7-amino-3-methoxymethyl-3-cephem-4-carboxylate hydrochloride (Isomer B) (411 mg) are suspended in methylene chloride (6 ml), pyridine (253 mg) is added thereto, and the resultant mixture is cooled to -15℃. A solution of phosphorus oxychloride (169 mg) in methylene chloride (1 ml) is dropwise added thereto, followed by stirring at the same temperature as above for 20 minutes. The reaction mixture is admixed with ethyl acetate, washed with dilute hydrochloric acid, 5 % aqueous sodium hydrogen carbonate solution and an aqueous sodium chloride solution in order, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue is washed with diisoproopyl ether and collected by filtration to give said objective compound (515 mg).

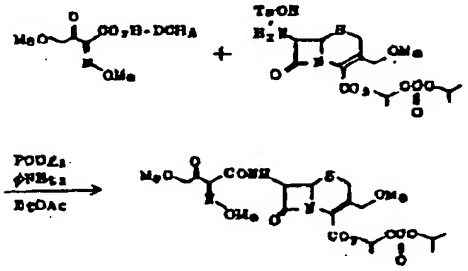
NMR (δ ppm, deuteroacetone):

1.28 (6 H , d , J = 6 Hz) , 1.53 (3 H , d , J = 5.5 Hz) , 2.28 (3 H , s) , 3.57 (2 H , s) , 3.84 (3 H , s) , 4.22 (2 H , s) , 4.83 (1 H , Sep , J = 6 Hz) , 5.14 (1 H , d , J = 5 Hz) , 5.38 (1 H , dd , J = 5 Hz , J = 8 Hz) , 5.96 (1 H , q , J = 5 Hz) , 7.34 (1 H , s) , 8.38 (1 H , d , J = 8 Hz) , 8.58 (1 H , s)

[2b]
The reaction is effected with the same amounts and reaction conditions as in [Example 2a] but using tetrahydrofuran as the solvent to give the above product (351 mg).

[2c]
The reaction is effected with the same amounts and reaction conditions as in [Example 2a] but using dicyclohexylamine (199 mg) and N,N-diethylaniline (328 mg) in place of pyridine to give the above product (494 mg).

[Example 3]



1-(Isopropyloxycarbonyloxy)ethyl 7-(4-methanesulonyloxy-(Z)-2-methoxyimino-3-oxobutyrylamino)-3-methoxymethyl-3-cephem-4-carboxylate (Isomer B based on the ester portion)

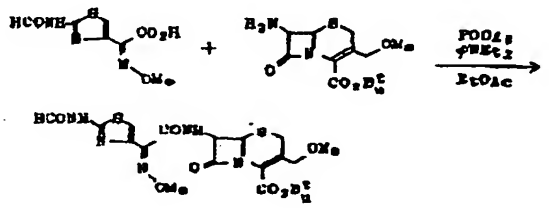
4-Methanesulfonyloxy-(Z)-2-methoxyimino-3-oxo-butyric acid dicyclohexylamine salt (4.42 g), 1-(isopropyloxycarbonyloxy)ethyl 7-amino-3-methoxymethyl-3-cephem-4-carboxylate p-toluenesulfonate (Isomer B) (5.47

g), N,N-diethylaniline (2.98 g), phosphorus oxychloride (1.61 g) and ethyl acetate (70 ml) are subjected to reaction in the same manner as in [Example 1], followed by post-treatment. Recrystallization from ethanol affords the above objective compound (5.46 g). M.P., 120~121℃.

NMR (δ ppm, deuterochloroform):

1.33 (9 H , s , J = 6 Hz) , 1.55 (3 H , d , J = 5.5 Hz) , 3.16 (3 H , s) , 3.30 (3 H , s) , 3.53 (2 H , s) , 4.14 (2 H , s) , 4.35 (1 H , Sep , J = 6 Hz) , 4.85 (1 H , d , J = 5 Hz) , 5.22 (2 H , s) , 5.76 (1 H , dd , J = 5 Hz , J = 9 Hz) , 6.87 (1 H , q , J = 5.5 Hz) , 7.12 (1 H , d , J = 9 Hz)

[Example 4]



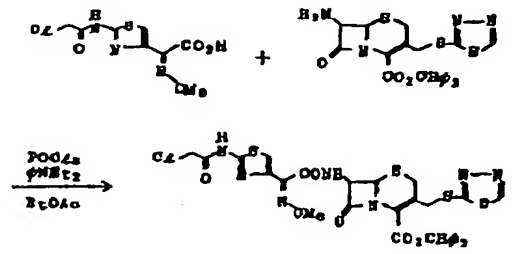
tert-Butyl 7-[2-(2-formylaminothiazol-4-yl)-(Z)-2-methoxyiminoacetamido]-3-methoxy-methyl-3-cephem-4-carboxylate

2-(2-Formylaminothiazol-4-yl)-(Z)-2-methoxyiminoacetic acid (378 mg), tert-butyl 7-amino-3-methoxymethyl-3-cephem-4-carboxylate (451 mg), N,N-diethylaniline (492 mg), phosphorus oxychloride (253 mg) and ethyl acetate (7 ml) are subjected to reaction in the same manner as in [Example 1], followed by post-treatment to give the above objective compound (664 mg). M.P., 140~156℃ (decomp.).

NMR (δ ppm, deutero-dimethylsulfoxide):

1.48 (3 H , s) , 3.28 (2 H , s) , 3.58 (2 H , s) , 3.87 (3 H , s) , 4.18 (2 H , s) , 5.12 (1 H , d , J = 5 Hz) , 5.76 (1 H , dd , J = 5 Hz , J = 8.5 Hz) , 7.34 (1 H , s) , 8.47 (1 H , s) , 9.62 (1 H , d , J = 8.5 Hz) , 12.52 (1 H , s)

[Example 5]

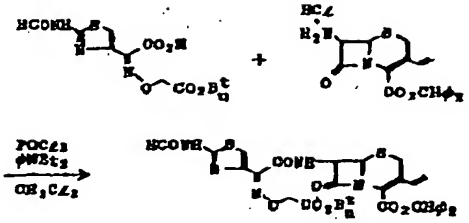


Diphenylmethyl 7-[2-(2-chloroacetamidothiazol-4-yl)-(Z)-2-methoxyiminoacetamido]-3-(1,3,4-thiadiazol-2-yl)thiomethyl-3-cephem-4-carboxylate

2-(2-Chloroacetamidothiazol-4-yl)-(Z)-2-methoxyiminoacetic acid (153 mg), diphenylmethyl 7-amino-3-(1,3,4-thiadiazol-2-yl)thiomethyl-3-cephem-4-carboxylate (248 mg), N,N-diethylaniline (187 mg), phosphorus oxychloride (85 mg) and ethyl acetate (5 ml) are subjected to reaction in the same manner as in [Example 1], followed by post-treatment to give the above objective compound (664 mg).
NMR (δ ppm, deutero-chloroform):

3.89 (2 H , s) , 3.98 (3 H , s) , 4.07 (2 H , s) , 4.38 (2 H , ABq , J = 14 Hz) , 5.03 (1 H , d , J = 5 Hz) , 5.92 (1 H , dd , J = 5 Hz , J = 8 Hz) , 6.88 (1 H , s) , 7.09 (1 H , s) , 7.17 (1 H , s) , 7.0 ~ 7.5 (10 H , m) , 7.94 (1 H , d , J = 8 Hz) , 8.85 (1 H , s)

[Example 6]

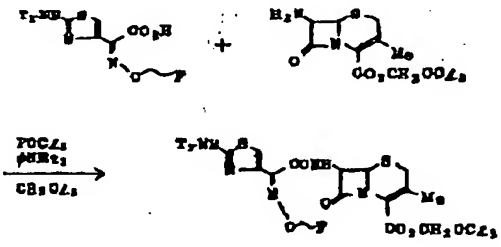


Diphenylmethyl 7-[2-(2-formylaminothiazol-4-yl)-(Z)-2-tert-butoxycarbonylmethoxy-iminoacetamido]-3-vinyl-3-cephem-4-carboxylate

2-(2-Formylaminothiazol-4-yl)-(Z)-2-tert-butoxycarbonylmethoxyiminoacetic acid (254 mg), diphenylmethyl 7-amino-3-vinyl-3-cephem-4-carboxylate hydrochloride (300 mg), N,N-diethylaniline (334 mg), phosphorus oxychloride (118 mg) and methylene chloride (5 ml) are subjected to reaction in the same manner as in [Example 2a], followed by post-treatment to give the above objective compound (451 mg).
NMR (δ ppm, deutero-chloroform):

1.42 (9 H , s) , 1.52 (2 H , s) , 4.62 (2 H , s) , 5.85 (1 H , d , J = 5 Hz) , 4.9 ~ 5.6 (3 H , m) , 5.85 (1 H , dd , J = 5 Hz , J = 9 Hz) , 6.80 (1 H , s) , 7.0 ~ 7.5 (10 H , m) , 7.38 (1 H , s) , 8.52 (1 H , s) , 8.74 (1 H , d , J = 8 Hz)

[Example 7]



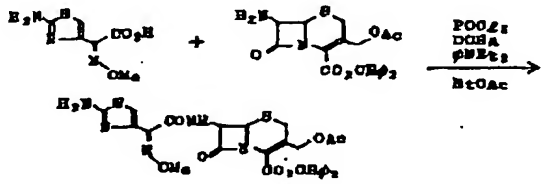
2,2,2-Trichloroethyl 7-[2-(2-tritylaminothiazol-4-yl)-(Z)-2-(2-fluoroethoxy)iminoacet-amido]-3-methyl-3-cephem-4-carboxylate

2-(2-Tritylaminothiazol-4-yl)-(Z)-2-(2-fluoroethoxy)iminoacetic acid (499 mg), 2,2,2-trichloroethyl 7-amino-3-methyl-3-cephem-4-carboxylate hydrochloride (350 mg), N,N-diethylaniline (463 mg), phosphorus oxychloride (161 mg) and methylene chloride (7 ml) are subjected to reaction in the same manner as in [Example 2a], followed by post-treatment to give the above objective compound (650 mg).

NMR (δ ppm, deutero-chloroform):

2.18 (3 H , s) , 3.38 (2 H , ABq , J = 18 Hz) , 4.23 (2 H , s) , 4.5 ~ 5.1 (2 H , m) , 4.88 (2 H , ABq , J = 12 Hz) , 4.98 (1 H , d , J = 5 Hz) , 5.78 (1 H , dd , J = 5 Hz , J = 8 Hz) , 6.93 (1 H , s) , 6.97 (1 H , d , J = 8 Hz) , 7.32 (18 H , s)

[Example 8]



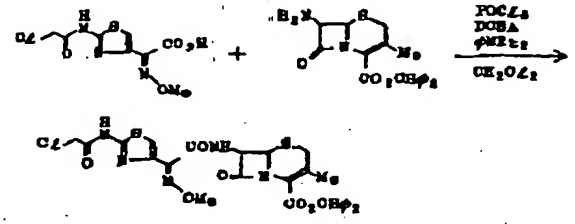
Diphenylmethyl 7-[2-(2-aminothiazol-4-yl)-(Z)-2-methoxyiminoacetamido]-3-acetoxymethyl-3-cephem-4-carboxylate

2-(2-Aminothiazol-4-yl)-(Z)-2-methoxyiminoacetic acid (254 mg), diphenylmethyl 7-amino-3-acetoxymethyl-3-cephem-4-carboxylate (503 mg), dicylohexylamine (228 mg), N,N-diethylaniline (344 mg), phosphorus oxychloride (192 mg) and ethyl acetate (15 ml) are subjected to reaction in the same manner as in [Example 2c], followed by column chromatography using silica gel to give the above objective compound (588 mg).

Developing solvent: n-hexane-ethyl acetate (1:2) → ethyl acetate.
NMR (δ ppm, deutero-chloroform):

1.92 (3 H , s) , 3.32 (2 H , s) , 3.87 (3 H , s) , 4.75 (2 H , ABq , J = 13 Hz) , 4.98 (1 H , d , J = 5 Hz) , 5.85 (1 H , s) , 5.98 (1 H , dd , J = 5 Hz , J = 8 Hz) , 6.59 (1 H , s) , 6.77 (1 H , s) , 7.17 (10 H , s) , 8.08 (1 H , d , J = 8 Hz)

[Example 9]

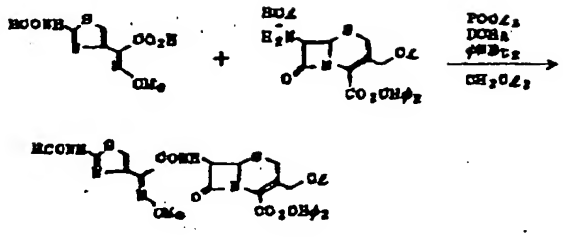


Diphenylmethyl 7-[2-(2-chloroacetamidothiazol-4-yl)-(Z)-2-methoxyiminoacetamido]-3-methyl-3-cephem-4-carboxylate

2-(2-Chloroacetamidothiazol-4-yl)-(Z)-2-methoxyiminoacetic acid (139 mg), diphenyl-methyl 7-amino-3-methyl-3-cephem-4-carboxylate (190 mg), dicylohexylamine (90.6 mg), N,N-diethylaniline (74.5 mg), phosphorus oxychloride (76.7 mg) and methylene chloride (3 ml) are subjected to reaction in the same manner as in [Example 2c], followed by post-treatment to give the above objective compound (295 mg).
NMR (δ ppm, deutero-chloroform):

2.08 (3 H , s) , 3.28 (2 H , ABq , J = 18 Hz) , 3.58 (2 H , s) , 4.02 (3 H , s) , 5.08 (1 H , d , J = 5 Hz) , 5.84 (1 H , dd , J = 5 Hz , J = 8 Hz) , 6.87 (1 H , s) , 6.94 (1 H , s) , 7.1 ~ 7.5 (10 H , m) , 8.28 (1 H , d , J = 8 Hz)

[Example 10]

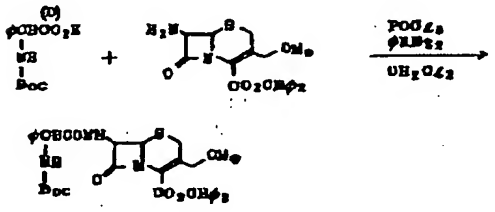


Diphenylmethyl 7-[2-(2-formylaminothiazol-4-yl)-(Z)-2-methoxyiminoacetamido]-3-chloromethyl-3-cephem-4-carboxylate

2-(2-Formylaminothiazol-4-yl)-(Z)-2-methoxyiminoacetic acid (532 mg), diphenyl-methyl 7-amino-3-chloromethyl-3-cephem-4-carboxylate hydrochloride (1.0 g), dicylohexylamine (422 mg), N,N-diethylaniline (661 mg), phosphorus oxychloride (337 mg) and methylene chloride (12 ml) are subjected to reaction in the same manner as in [Example 2c], followed by post-treatment to give the above objective compound (1.084 g).
NMR (δ ppm, deutero-dimethylsulfoxide):

3.97 (2 H , s) , 3.98 (3 H , s) , 4.44 (2 H , s) , 5.25 (1 H , d , J = 5 Hz) , 5.84 (1 H , dd , J = 5 Hz , J = 9 Hz) , 6.94 (1 H , s) , 7.1 ~ 7.6 (16 H , m) , 7.48 (1 H , s) , 8.46 (1 H , s) , 8.75 (1 H , d , J = 9 Hz)

[Example 11]



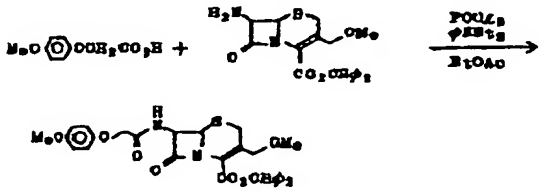
Diphenylmethyl 7-(D- α -tert-butoxybarbonylaminophenylacetamido)-3-methoxymethyl- 3-cephem-4-carboxylate

D-α-tert-Butoxycarbonylaminophenylacetic acid (276 mg), diphenylmethyl 7-amino-3-methoxymethyl-3-cephem-4-carboxylate (410 mg), N,N-diethylaniline (373 mg), phosphorus oxychloride (169 mg) and methylene chloride (7 ml) are subjected to reaction in the same manner as in [Example 2a], followed by post treatment to give the above objective compound (461 mg).

NMR (δ ppm, deutero-chloroform):

1.48 (9 H , s) , 3.18 (3 H , s) , 3.34 (2 H , s) , 4.14 (2 H , s) , 4.81 (1 H , d , J = 4.5 Hz) , 5.17 (1 H , d , J = 8 Hz) , 5.72 (1 H , dd , J = 4.5 Hz , J = 8 Hz) , 6.84 (1 H , d , J = 8 Hz) , 6.95 (1 H , s) , 7.0 ~ 7.5 (16 H , m)

[Example 12]



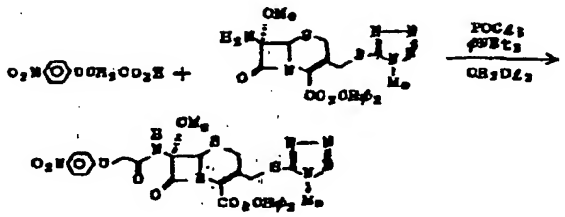
Diphenylmethyl 7-(4-methoxyphenoxy)acetamido-3-methoxymethyl-3-cephem-4-carboxylate

4-Methoxyphenoxyacetic acid (200 mg), diphenylmethyl 7-amino-3-methoxymethyl-3-cephem-4-carboxylate (410 mg), N,N-diethylaniline (373 mg), phosphorus oxychloride (169 mg) and ethyl acetate (7 ml) are subjected to reaction in the same manner as in [Example 2c], followed by post-treatment to give the above objective compound (550 mg).

NMR (δ ppm, deutero-chloroform):

3.14 (3 H , s) , 3.44 (2 H , s) , 3.88 (3 H , s) , 4.17 (2 H , s) , 4.62 (2 H , s) , 4.98 (1 H , d , J = 5 Hz) , 5.88 (1 H , dd , J = 5 Hz , J = 9 Hz) , 6.75 (4 H , s) , 6.87 (1 H , s) , 7.2 ~ 7.5 (10 H , m)

[Example 13]

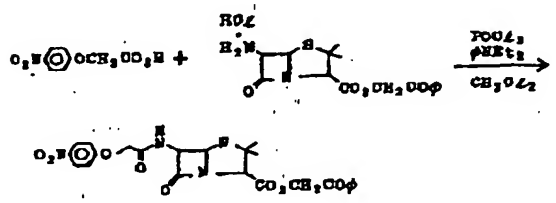


Diphenylmethyl 7 β -(4 -nitrophenoxy)acetamido-7 α -methoxy-3-(1-methyl-1H-tetrazol-5-yl)thiomethyl-3-cephem-4-carboxylate

4-Nitrophenoxyacetic acid (118 mg) and N,N-diethylaniline (179 mg) are dissolved in methylene chloride (3 ml) and cooled at -10℃. Phosphorus oxychloride (92 mg) is dropwise added thereto, followed by stirring for 5 minutes. Then, a solution of diphenylmethyl 7 β -amino-7 α -methoxy-3-(1-methyl-1H-tetrazol-5-yl)thiomethyl-3-cephem-4-carboxylate (262 mg) in methylene chloride (2 ml) is dropwise added thereto, and stirring is effected for 1 hour. The reaction mixture is admixed with ethyl acetate, washed with dilute hydrochloric acid, a 5% aqueous solution of sodium hydrogen carbonate and an aqueous sodium hydrochloride solution in order, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue is purified by column chromatography on silica gel to give the above objective compound (44 mg).
Developing solvent: ethyl acetate-cyclohexane (1:1).
NMR (δ ppm, deutero-chlorofororm):

1.52 (3 H , s) , 2.58 (2 H , s) , 3.78 (2 H , s) , 4.48 (2 H , ABq , J = 13 Hz) , 4.63 (2 H , s) , 5.03 (1 H , s) , 6.84 (1 H , s) , 6.95 (2 H , d , J = 8Hz) , 7.3 ~ 7.8 (11 H , m) , 8.13 (2 H , d , J = 9 Hz)

[Example 14]

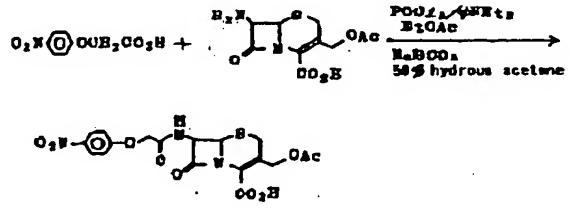


Phenacyl 6-(4-nitrophenoxy)acetamidopenicillanate

Reaction is carried out in the same manner as in [Example 2a] using 4-nitrophenoxyacetic acid (207 mg), phenacyl 6-aminopenicillanate hydrochloride (371 mg), N,N-diethylaniline (463 mg), phosphorus oxychloride (161 mg) and methylene chloride (7 ml), followed by post-treatment to give the above objective compound (430 mg).
NMR (δ ppm, deutero-chlorofororm):

1.53 (6 H , s) , 4.54 (1 H , s) , 4.61 (3 H , s) , 5.38 (2 H , ABq , J = 14 Hz) , 5.4 ~ 5.8 (2 H , m) , 5.8 ~ 6.2 (6 H , m) , 8.53 (2 H , d , J = 9 Hz) , 8.11 (2 H , d , J = 9 Hz)

[Example 15]

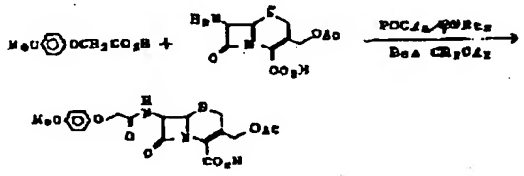


7-(4-Nitrophenoxy)acetamido-3-acetoxymethyl-3-cephem-4-carboxylic acid

4-Nitrophenoxyacetic acid (434 mg) is suspended in ethyl acetate (4 ml), and N,N-diethylaniline (298 mg), followed by cooling to -10℃. Phosphorus oxychloride (337 mg) is dropwise added thereto, followed by stirring for 5 minutes. The resulting mixture is added to a solution of 7-aminocephalosporanic acid (545 mg) and sodium hydrogen carbonate (840 mg) in 50 % hydrous acetone (14 ml) while cooling with ice, and stirring is continued for 1 hour. The reaction mixture is concentrated under reduced pressure to remove acetone, admixed with a 5 % aqueous solution of sodium hydrogen carbonate and washed with ethyl acetate. To the aqueous phase, ethyl acetate is added, and conc. hydrochloric acid is added dropwise while stirring to make pH 2. The organic phase is separated, dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give the above objective compound (630 mg).
NMR (δ ppm, deutero-dimethylsulfoxide):

2.05 (3 H , s) , 3.58 (2 H , s) , 4.78 (2 H , s) , 4.87 (2 H , ABq , J = 13 Hz) , 5.09 (1 H , d , J = 5 Hz) , 5.70 (1 H , dd , J = 5 Hz , J = 8 Hz) , 7.08 (2 H , d , J = 8 Hz) , 8.16 (2 H , d , J = 8 Hz) , 8.18 (1 H , d , J = 8 Hz)

[Example 16]



7-(4-Methoxyphenoxy)acetamido-3-acetoxymethyl-3-cephem-4-carboxylic acid

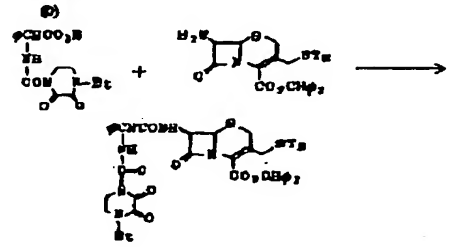
7-Aminocephalosporanic acid (545 mg) is suspended in anhydrous methylene chloride (7 ml) and cooled with ice. N,O-Bistrimethylsilylacetamide (1.03 mg) is dropwise added thereto, and stirring is continued at room temperature for 50 minutes. Separately, 4-methoxyphenoxyacetic acid (401

mg) is dissolved in anhydrous methylene chloride (5 ml), and N,N-diethylaniline (298 mg) is added thereto, followed by cooling to -10℃. Phosphorus oxychloride (337 mg) is dropwise added thereto, followed by stirring for 5 minutes. The resulting mixture is added to the previously obtained mixture at -10℃, and stirring is continued for 30 minutes. After concentration under reduced pressure, ethyl acetate is added thereto, and the resulting mixture is washed with 5 % hydrochloric acid twice and aqueous sodium chloride solution once, dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give the above objective compound (730 mg).

NMR (δ ppm, deutero-dimethylsulfoxide):

[illegible]

[Example 17]



Diphenylmethyl 7-[D-[2-(2,3-dioxo-4-ethylpiperazin-1-yl)carbonylamino]phenylacetamido]-3-(1-methyl-1H-tetrazol-5-yl)thiomethyl-3-cephem-4-carboxylate

Diphenylmethyl 7-amino-3-(1-methyl-1H-tetrazol-5-yl)thiomethyl-3-cephem-4-carboxylate (241 mg), D-[2-(2,3-dioxo-4-ethylpiperazin-1-yl)carbonylamino]phenylacetic acid (160 mg) and N,N-diethylaniline (164 mg) are dissolved in methylene chloride (10 ml) and cooled to -10℃. Phosphorus oxychloride (77 mg) is dropwise added thereto, and stirring is

effected at the same temperature as above for 20 minutes. The reaction mixture is admixed with ethyl acetate, washed with dilute hydrochloric acid, a 5% aqueous solution of sodium hydrogen carbonate and an aqueous sodium hydrochloride solution in order, dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give the above objective compound (372 mg).

NMR (δ ppm, deutero-chlorofororm):

1.07 (3 H , t , J = 7 Hz) , 3.0 ~ 4.2 (8 H , m) , 3.75 (3 H , s) , 4.32 (2 H , s) , 4.84 (1 H , d , J = 5 Hz) , 5.5 ~ 5.9 (2 H , m) , 6.83 (1 H , s) , 7.1 ~ 7.7 (15 H , m) , 8.01 (1 H , d , J = 8 Hz) , 8.07 (1 H , d , J = 7 Hz)